AstraZeneca

Clinical Study Report

Drug Substance	Esomeprazole
Study Code	D9914C00002
Date	11 February 2008

A single-blind single arm study to validate the Reflux Disease Questionnaire (RDQ) for the diagnosis of reflux disease in primary care in patients treated with esomeprazole 40 mg o.d.

Study dates:	First patient enrolled: 19 September 2005 Last patient completed: 31 October 2006
Phase of development:	IV
International Co-ordinating Investigator:	
Sponsor's Responsible Medical Officer:	

This study was performed in compliance with Good Clinical Practice.

Drug Product	Esomeprazole	**SYNOPSIS**	
Drug Substance	Esomeprazole		
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A single-blind single arm study to validate the Reflux Disease Questionnaire (RDQ) for the diagnosis of reflux disease in primary care in patients treated with esomeprazole 40 mg o.d.

Study centre(s)

The study was conducted at in total 6 countries involving 73 Primary Care Physician centres and 22 Secondary Care Physician centres; (8/3 in Canada, 26/7 in Germany, 6/4 in Denmark, 7/1 in Norway, 19/5 in Sweden and 7/2 in the United Kingdom).

Publications

An abstract of the main study result was presented at the 2007 UEGW in Paris.

Study dates		**Phase of development**
First patient enrolled	19 September 2005	Therapeutic use (IV)
Last patient completed	23 November 2006	

Objectives

Primary objective

The primary objective of this study was to determine the accuracy of the Reflux Disease Questionnaire (RDQ) as a diagnostic test for gastroesophageal reflux disease. Symptom evaluation by the RDQ was to be compared with other established approaches to the diagnosis of gastroesophageal reflux disease (GERD) in a primary care patient population with symptoms thought to be of upper gastrointestinal (GI) tract origin.

In this exercise, different pre-specified combinations of the RDQ symptoms were to be tested primarily using receiver operating characteristics (ROC) analysis. An optimal selection of RDQ items was determined by using discriminant analysis techniques (more details are specified in the Statistical Analysis Plan (StAP)). The momost accurate aggregate score selected at this step, with its cut-off level, served for the analyses planned in secondary objectives.

Secondary objectives

1. To estimate the sensitivity and specificity of the selection of RDQ items, endoscopy, esophageal pH monitoring, response to proton pump inhibitors (PPIs) and Symptom Association Probability (SAP) as diagnostic tests for GERD by using Latent Class Analysis (LCA) and Bayesian statistics

2. To estimate the prevalence of GERD with LCA and Bayesian statistics

3. To describe the study population at the initial and last visit with the Gastrointestinal Symptom Rating Scale (GSRS) dimensions in the whole study population and by GERD diagnosis

4. To estimate responsiveness of the RDQ during therapy in patients categorised as having or not having GERD

Exploratory objectives

1. To explore the burden of illness over the study period by using the GERD Impact Scale (GIS) questionnaire.

2. To examine the association between histological markers in the esophageal epithelium and the diagnosis of GERD/no GERD.

The association between histological markers and the diagnosis of GERD/no GERD will be be separately reported.

Study design

This was a non-comparative, single-blind, multi-centre, international study.

Target patient population and sample size

Patients were of either gender aged 18-79 years, inclusive, with symptoms thought to arise from the upper gastrointestinal tract. The symptoms must have been present for at last 4 weeks prior to Visit 1 and have occurred at least twice a week during that period. During the last week prior to Visit 1, symptoms had to be at least of mild severity for a minimum of 3 days.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

This was a non-comparative study.

Placebo was taken orally once daily in the morning prior to breakfast (only during the placebo period of the study). Esomeprazole 40 mg capsules were taken orally once daily prior to breakfast (only during the active treatment period of the study).

Duration of treatment

Placebo was taken for a maximum of 10 days followed by esomeprazole for a maximum of 17 days.

Criteria for evaluation (main variables)

Efficacy

Primary outcome variable:

- Presence/absence of GERD as assessed by endoscopic Los Angeles (LA) grade, pH monitoring (% time with esophageal pH<4), SAP, outcome of PPI test.

Secondary outcome variables:

- Occurrence and severity of clinical symptoms at the initial and last visit

Patient reported outcomes (PROs)

Primary outcome variable:

- RDQ items at baseline.

Secondary outcome variables:

- RDQ item scores and RDQ mean item scores for RDQ dimensions at baseline and at the end of treatment.
- -Mean item score for the GSRS dimensions at the initial and last visit

Exploratory variables

- GERD Impact Scale (GIS) item scores over the study period
- Scores and values for histological markers (not reported in this CSR)

Safety

Only serious adverse events (SAEs) and those adverse events (AEs) causing premature discontinuation of active treatment (esomeprazole 40 mg od) were recorded (descriptive analysis).

Genetics (optional)

DNA samples were obtained for explorative research into genes that may influence the diagnosis, prognosis, etiology of, or susceptibility to GERD and associated disease and/or disposition, efficacy, safety and tolerability to esomeprazole under investigation in this study. All patients enrolled into this main study were invited to participate in an additional genetic research component to this study. Results of the genetic analyses are not included in this report and will be reported separately.

Statistical methods

The primary analyses are based on the evaluable patient population (ITT population), including all patients who have completed the RDQ at Screening , and who have performed at least 3 of the 4 diagnostic procedures. Patients with a LA Grade D confirmed by endoscopy were included in evaluable patient population independent from the number of diagnostic procedures. Patients with at least one major violation (see Section 2.2 of the StAP) were considered as *non-evaluable* for the primary analysis and were excluded from the evaluable patient population population. The reason for this exclusion was related to the fact, that patients with at least one of these violations do not provide sufficient and/or reliable information to the primary analysis.

Different pre-specified combinations of the RDQ items were evaluated against the diagnosis of GERD using ROC analysis. For each selection of RDQ items, cut-offs that optimise sensitivity, specificity and efficiency were calculated. The diagnosis of GERD was based on endoscopy, pH monitoring, SAP, and outcome of a PPI test. Latent Class Analysis (LCA) and Bayesian analysis was used as alternative ways to estimate the prevalence of GERD, and to estimate the sensitivity and specificity of the optimal selection of RDQ items for efficiency and the various measures used for GERD diagnosis.

Patient population

Out of 507 enrolled patients, 481 patients (94.1%) took at least one dose of investigational product (placebo and/or esomeprazole) and 426 (84.0%) patients took at least one dose of esomeprazole. Three-hundred and eighty-eight patients (76.5%) completed the study.

Three-hundred and eight of 507 enrolled patients (60.7%) did not have any major violation and were belonging to the Evaluable Patient Population used in the primary analysis. Based on the evaluable patients, 203 patients (65.9%) were classified as having GERD according to the diagnosticcriteria pre-specified in the study protocol.

The demographic and baseline characteristics of the study population are described in Table S 1.

Table S 1 Demographics and baseline characteristics (ITT population)

Baseline characteristic		No GERD (n=105)	GERD (n=203)	Total (n=308)
Gender	Male	27(25.7%)	116(57.1%)	143(46.4%)
	Female	78(74.3%)	87(42.9%)	165(53.6%)
Age (yrs)	Mean	45.3	47.7	46.9
	SD	15.8	13.1	14.1
	Min	18	18	18
	Max	74	76	76
Race	Caucasian	98(93.3%)	200(98.5%)	298(96.8%)
	Black	6(5.7%)	2(1.0%)	8(2.6%)
	Oriental	1(1.0%)	1(0.5%)	2(0.6%)
BMI (kg/m^2)	Mean	25.1	27.4	26.6
	SD	4.4	4.5	4.5
	Min	16	16	16

Table S 1 Demographics and baseline characteristics (ITT population)

Baseline characteristic		No GERD (n=105)	GERD (n=203)	Total (n=308)
	Max	36	46	46
LA grade	None	105(100.0%)	87(42.9%)	192(62.3%)
	Grade A	0(0.0%)	59(29.1%)	59(19.2%)
	Grade B	0(0.0%)	49(24.1%)	49(15.9%)
	Grade C	0(0.0%)	6(3.0%)	6(1.9%)
	Grade D	0(0.0%)	2(1.0%)	2(0.6%)
Barretts oesophagus	No	104(99.0%)	194(95.6%)	298(96.8%)
	Yes	1(1.0%)	9(4.4%)	10(3.2%)
Stricture	No	105(100.0%)	201(99.0%)	306(99.4%)
	Yes	0(0.0%)	2(1.0%)	2(0.6%)
Hiatal hernia	No	77(73.3%)	111(54.7%)	188(61.0%)
	Yes	28(26.7%)	92(45.3%)	120(39.0%)
Oesophagus, abnormal finding(s)	No	103(98.1%)	192(94.6%)	295(95.8%)
	Yes	2(1.9%)	11(5.4%)	13(4.2%)
Stomach, ulcer(s)	No	104(99.0%)	199(98.0%)	303(98.4%)
	Yes	1(1.0%)	4(2.0%)	5(1.6%)
Stomach erosion(s)	No	87(82.9%)	171(84.2%)	258(83.8%)
	Yes	18(17.1%)	32(15.8%)	50(16.2%)
Stomach, abnormal finding(s)	No	83(79.0%)	158(77.8%)	241(78.2%)
	Yes	22(21.0%)	45(22.2%)	67(21.8%)
Duodenum, ulcer(s)	No	105(100.0%)	199(98.0%)	304(98.7%)
	Yes	0(0.0%)	4(2.0%)	4(1.3%)
Duodenum erosion(s)	No	101(96.2%)	189(93.1%)	290(94.2%)
	Yes	4(3.8%)	14(6.9%)	18(5.8%)
Duodenum, abnormal finding(s)	No	99(94.3%)	186(91.6%)	285(92.5%)
	Yes	6(5.7%)	17(8.4%)	23(7.5%)
LA grade in (A,B,C,D)	No	105(100.0%)	87(42.9%)	192(62.3%)
	Yes	0(0.0%)	116(57.1%)	116(37.7%)
Time with ph< 4 > 5.5% during 24 h	No	105(100.0%)	68(33.5%)	173(56.2%)
	Yes	0(0.0%)	135(66.5%)	135(43.8%)
SAP≥95%	No	105(100.0%)	152(74.9%)	257(83.4%)
	Yes	0(0.0%)	51(25.1%)	51(16.6%)
PPI test needed and feasible	No	105(100.0%)	182(89.7%)	287(93.2%)
	Yes	0(0.0%)	21(10.3%)	21(6.8%)
H.p. status	Negative	80(76.2%)	155(76.4%)	235(76.3%)
	Positive	24(22.9%)	47(23.2%)	71(23.1%)
	Not evaluable	0(0.0%)	1(0.5%)	1(0.3%)
	Missing	1(1.0%)	0(0.0%)	1(0.3%)
Total time (%) with ph<4	Mean	1.3	8.1	5.8
	SD	1.0	5.8	5.7
	Min	0	0	0
	Max	3	40	40
History of symptoms of reflux disease	No	36(34.3%)	29(14.3%)	65(21.1%)
	Yes	69(65.7%)	174(85.7%)	243(78.9%)

ITT=Intention to treat LA=Los Angeles classification for reflux disease SAP=Symptom association probability H.p.=Helicobacter pylori

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Efficacy and patient-reported outcome (PRO) results

The pre-spefied combination #2 of items in the RDQ did most accurately diagnose GERD. A reduction in symptoms, based on RDQ, GSRS and GIS scores, from baseline to last visit was observed in both GERD and non-GERD patients

Safety results

In this study, only AEs causing premature discontinuation of study drug occurring from the time of first administration of active treatment (esomeprazole 40 mg od) until the end of the study period were to be collected and recorded. All SAEs were to be recorded from the time of signed Informed Consent to the end of the study.

Few adverse events (AEs) were reported in this study (Table S 2). Three patients had SAEs, 2 occurred during placebo treatment and one 19 days after last dose of esomeprazole. Five patients discontinued study therapy due to AE and 2 of these patients also discontinued from the study. Eosomeprazole was well tolerated.

Table S 2 Number of patients who had an adverse event in any category (Safety population)

Category of adverse event[a]	Placebo (n=481)	Esomeprazole 40 mg (n=426)
Any adverse event	2[b]	5
Serious adverse event	2	1
Discontinuation of study treatment due to AE	1	4
AE caused patient to discontinue study	1	1

[a]Patients with multiple events in the same category are only counted once in that category
[b]The AE stop date for patient E0504017 is 2 days after 1st intake of esomeprazole treatment

D9914C00002_C00010_AE

Date of the report

11 February 2008